REMARKS/ARGUMENTS

I. Status of Claims

Claims 1-9 were previously canceled.

Claims 10-11, 15 and 17 are withdrawn.

Claims 12, 14, and 18 are amended.

Claims 12-14, 16 and 18 are pending.

II. Priority

Applicants herein provide a certified translation of the Japanese language priority document JP 2003-354503, filed October 15, 2003. Applicants request the benefit of foreign priority under 35 USC §119(a)-(d).

III. Specification

In compliance with 37 CFR §§ 1.52 and 1.125, applicants herein submit a marked-up and a clean version of the substitute specification to correct non-idiomatic English language. No new matter has been introduced by way of these amendments.

IV. Pending claims satisfy 35 USC §112 second paragraph requirements

The examiner has rejected claims 12-14, 16 and 18 under §112 second paragraph for being indefinite. Claim 12 is amended.

It appears that at least some of the 112 rejections have been raised in part due to an incomplete understanding of the invention as claimed. Briefly, as illustrated to a greater detail in the specification, drawings, and summarized herein, even when a sample containing a target molecule (to be detected) is treated with an inert substance-immobilized solid phase carrier, the target molecule remains in the supernatant, because it does not bind to the solid phase carrier. By treating the supernatant with a ligand-immobilized solid phase carrier, the target molecule binds to the solid phase carrier and accordingly, an extract of the solid phase carrier (first extract) contains the target molecule.

On the other hand, by treating a sample containing the target molecule with a ligand-immobilized solid phase carrier, the target molecule binds to the solid phase carrier, and the remaining supernatant does not contain the target molecule. Even when the supernatant is treated again with the ligand-immobilized solid phase carrier, because the target molecule is not contained in the supernatant, there is no binding of the target molecule to the solid phase carrier and subsequently, there is no detection of the target molecule in the extract (second extract). A target

molecule that is detected in the first extract, but not detected or detected at a considerably low level in the second extract is considered as the specific target molecule.

The problems of the conventional antagonistic methods such as insufficient dissolution of a free-ligand used for antagonizing and denaturation of protein due to the addition of a large amount of a ligand have been improved in the present invention.

In response to the examiner's objections regarding the clarity of some of the limitations of claim 12, applicants provide the following explanations:

(i) The inert substance does not have binding affinity to the target molecule as compared to the ligand. A ligand has a binding affinity to the target molecule and, as a control, if the target molecule is specific to the ligand, then an inert substance does not have a binding affinity to the molecule. In the present invention, two kinds of solid phase carriers are used: a ligand-immobilized solid phase carrier and an inert substance-immobilized solid phase carrier to determine whether the target molecule-ligand binding is specific.

(ii) The inert substance and the ligand do not bind different epitopes present in the target molecule so as to form a sandwich format. The inert substance is immobilized on a solid-phase carrier, and the ligand is also immobilized on a solid-phase carrier. Since the inert substance does not have a specific binding affinity to the target molecule, it cannot form a sandwich structure. Even when treated with an inert substance-immobilized solid-phase carrier, the target molecule contained in a sample does not bind to the carrier (a nonspecifically-absorbing substance is removed).

(iii) The specific complexes that are expected to be formed include the formation of "a solid phase carrier-ligand-target molecule complex".

(iv) A separation step to separate bound from unbound components is described by the step of extracting the target molecule bound to the ligand immobilized on the solid phase carrier to obtain a ligand-immobilized solid phase carrier first extract. In addition, as shown in FIG. 2, a first step to separate components bound to the inert substance-immobilized solid phase carrier from the unbound components is performed. The target molecule does not bind to the inert substance-immobilized solid phase carrier. A step to separate components bound to the ligand-immobilized solid phase carrier from the unbound components is performed. The target molecule is a component bound to the ligand-immobilized solid phase carrier.

(v) Depending on the specificity of the target-ligand binding, there may be more than one target molecule for binding the ligand, as long as they do not substantially bind to the inert substance.

(vi) The examiner stated that "Claim 12, step (iii) is confusing because it is unclear how a molecule bound to ligand immobilized to solid phase is extracted, i.e. from the ligand-immobilized to solid phase, to thus obtain "ligand-immobilized solid phase extract 1". It is specifically unclear why the "extract 1" which contains the "extracted molecule" still comprises "ligand-immobilized solid phase". In response, applicants amended the claim to remove the reference to "ligand-immobilized solid phase" to improve clarity. The target molecule can be extracted from the ligand-immobilized solid phase carrier according to any suitable method that is generally employed for extracting a protein bound on a solid phase carrier, including for example, extraction using a detergent and the like.

On page 5 of the Action, it appears that the Examiner interprets "extracting" as "separation between bound and unbound components". Claim 12 is amended to clarify that the extraction step relates to a separation of the target molecule from the solid-phase carrier.

On page 5 of the Action, the Examiner questions whether the ligands in steps (iv) and (v) are the same. As explained above, the ligands used in the various steps are the same and the method determines whether the ligand-target binding is specific.

On page 6 of the Action, the Examiner stated that claim 12 is indefinite because it is unclear how the comparing and analyzing step in (vii) and identifying step in (viii) are performed since the nature of the resulted products is not clearly defined. In response, applicants state that the comparing and analyzing steps are performed using methods generally known in the art. For example, as stated in page 12, lines 5-12 of the specification, the analysis step can employ an ordinary method of protein analysis. For example, analysis by SDS-PAGE is an option. Any suitable detection technique for the target molecules can be readily ascertained a person of ordinary skill in the art. By subjecting the first extract and the second extract to any suitable detection analysis under the same conditions, and comparing the results obtained, target molecule differences in the individual extracts can be examined.

On page 7 of the Action, with respect to claim 14, the Examiner points out that "structurally similar" is indefinite. Generally, as understood in the art, a "structurally similar compound" means a compound which is not structurally the same, but shares similar structural features. The

specification on page 13, line 32- page 14, line 6 state that "provided [structural] information on the structure-activity relationship of the ligand is available in advance and utilizable, it is possible to select an inert substance as appropriate according to the information, and prepare a solid phase carrier wherein the inert substance is immobilized. Meanwhile, if no such information is available in advance, a hydrophobic substance expected to normally produce non-specific protein adsorption may be immobilized." Therefore, based on the guidance in the specification and as understood in the art, a person of ordinary skill in the art would be able to interpret what structurally similar means reasonable clarity.

The term "subject ligand" in claim 14 is amended to "the ligand" to overcome the antecedent objection on page 7 of the Action. Claim 18 is amended to rectify the antecedent objection. Calculating the binding constant for the target molecule-ligand binding in claim 18 is the same for the various occurrences in claim 12.

V. Claims 12, 14, 16, and 18 are novel over Lindmo (U.S. Pat. No. 5,585,241) under 35 USC §102(b) second paragraph requirements

The examiner has rejected claims 12-14, 16 and 18 under §102(b) as being anticipated by Lindmo reference.

Lindmo teaches a sample portion (first sample portion) containing the desired molecule, which is treated with a predetermined amount of solid phase carriers having immobilized thereto a ligand having affinity for the molecule; thus, forming a first treated sample. The first treated sample is further treated with a different set of predetermined amount of solid phase carriers having immobilized thereto a ligand analog that has affinity for the molecule; thus, forming a first twice-treated sample. The two different sets of ligand carrying solid phase carriers are distinguishable from each other by flow cytometry. Each one ligand carrying solid phase particle carries a ligand or a ligand analog. The ligand and the ligand analogue have the same binding specificity but different binding affinity for the molecule and are independently and simultaneously detected. Another portion of the sample may also be treated with another distinguishable solid phase carrier having immobilized thereto an inert substance (irrelevant antibody) so as to form a second treated sample. Furthermore, steps for extracting and analyzing the molecule bound to the solid phase carrier may be present. The reference includes a ligand-immobilized solid phase carrier treatment and a ligand analog-immobilized solid phase carrier treatment. The ligand and the ligand analog have the same specificity but different binding affinity for the target molecule in a sample, and they can be simultaneously measured by utilizing the difference in the binding affinity.

To the contrary, in the pending claims, the ligands bound to the solid phase carriers are the same. The target molecule in the sample is consumed by the first treatment with a ligand-immobilized solid phase carrier, and does not remain in the sample at the time of the second treatment with the same ligand-immobilized solid phase carrier. Furthermore, a treatment with an inert substance-immobilized solid phase carrier is a required step in the pending claims, since it plays the role as a comparison step.

In Lindmo reference, an analyte and a binding partner thereof are known to specifically bind to each other (i.e., such combination is selected). In the pending claims, however, it is to be determined whether the binding of a target molecule to a ligand immobilized on a solid phase carrier is specific. A method of determining the specificity of the binding between the target molecule and the ligand is what the pending claims cover. The cited reference Lindmo does not teach all the limitations as recited in the pending claims.

An anticipating prior art reference should disclose each and every limitation of the claim expressly or inherently. *Akamai Techs. v. Cable & Wireless Internet Servs.*, 344 F.3d 1186, 1192 (Fed. Cir., 2003). To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter. *PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996). To serve as an anticipating reference, a reference must enable that which it is asserted to anticipate. *Elan Pharms., Inc. v. Mayo Found.*, 346 F.3d 1051, 1054 (Fed. Cir., 2003). The dispositive question regarding anticipation is whether one skilled in the art would reasonably understand or infer from the prior art reference's teaching that every claim limitation was disclosed in that single reference. *Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1368 (Fed. Cir. 2003) (*internal quotation marks and alterations omitted*).

Lindmo fails to teach each and every limitation of claims 12, 14, 16, and 18 and therefore does not anticipate these claims.

VI. Claim 13 is not obvious over Lindmo in view of Higgs et al. (U.S. Pat. No. 5,880,177)

As discussed in section V above, Lindmo fails to teach each and every limitation of claim 12 and therefore does not anticipate claim 12. Because stearic acid is a non-specific compound used as an inert substance. Lindmo teaches only specific ligands with known specificity and therefore, there is no conceivable reason to combine Higgs with Lindmo.

A determination of obviousness requires that "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved." *KSR International Co. v. Teleflex, Inc.*, -- U.S., 127 S.Ct. 1727, 1734, 82 U.S.P.Q.2d 1385 (2007) *quoting Graham v. John Deer Co.*, 383 U.S. 1, 17 (1966). In making a determination of obviousness by looking at the teachings of multiple patents, one should consider

> the effects of demands known to the design community or present in the market place; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit.
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> *KSR*, 127 S.Ct. at 1740-41 (*emphasis added*).

"[A] patent composed of several elements is not proved obvious merely by demonstrating the each of its elements was, independently, known in the prior art." *Id.* at 1741.

Therefore, applicants request withdrawal of the §103(a) rejection for claim 13.

If there are any remaining issues, applicants' representative welcomes the Examiner to contact the undersigned by telephone to resolve any pending matter. It is believed that no fees are due at this time. However, please charge any fees that might be due in connection with this submission to our Deposit Account No. 12-0913 with respect to our matter number 43512-104209.

Respectfully submitted,

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